REMARKS

Claims 1-6 are pending. Claims 7-18 are cancelled pursuant to a restriction requirement and without prejudice to the prosecution of their subject matter in another patent application.

The claims are amended to advance prosecution and without prejudice to the prosecution of subject matter cancelled by amendment in other patent applications. None of the amendments constitute new matter. Specifically, the amendment of claim 1 to recite "maternal blood sample" is supported by the specification at page 2 lines 4-7; the amendment of claim 1 to recite "an interior comprising a movable outer portion and a movable inner portion" is supported by the specification at page 4 lines 7-9; the amendment of claim 1 to recite "surface bearing a ligand specific for the fetal cells" is supported by the specification at page 2 lines 4-7 and page 5 lines 29-31; the amendment of claim 1 to recite "by alternately moving the outer portion and inner portion of the vessel relative to each other so as to repeatedly switch from one laminar flow to another" is supported by the specification at page 4 line 33 through page 5 line 3 and page 3 lines 24-25; the amendment of claim 1 to recite " duration of time effective for binding fetal cells to the ligand " is a limitation that ensures operability of the claimed subject matter and is implicit in the disclosure; the amendment of claim 2 to recite "rotatable" is supported by the specification at page 4 lines 7-9; the amendment of claim 2 to recite "distinct rather than coincident" is supported by the specification at page 5 lines 10-11; the deletion of "parallel" in claim 2 is supported by the specification at page 5 lines 7-19, which indicate that the situation where the axes are parallel is but one embodiment of the invention (*e.g.*, page 5 lines 17-19 disclose that chaotic flow may be three dimensional,

which would be consistent with elements rotated along non-parallel axes); and the amendment to claim 6 to replace "dipped into" with "immersed in" is supported by the specification at page 4 lines 1-2.

Original claims 1 and 2 are rejected under 35 U.S.C. §103(a). For reasons set forth in detail below, this rejection should be removed.

Original claims 3-6 are objected to as being dependent upon a rejected base claim, but are otherwise considered allowable. In view of the arguments presented and amendments to claims 1 and 2, it is requested that all the pending claims be deemed allowable.

1. The Claims Are Not Obvious Over Simons

Claims 1 and 2 are rejected under 35 U.S. C. §103(a) as being obvious over United States Patent No. 5,447,842 by Simons ("Simons"). According to the Examiner:

> The Simons patent discloses the various methods for separating fetal cells from maternal cells including binding one of the cell types to a immobilized antigen. The immobilized antigen can be placed on beads in the container or the antigen can be immobilized on the interior surface of the container (see col 10, lines 5-18). The reference is silent as to incurring "chaotic flow" to induce contact. However, in the absence of unexpected results one skilled in the art would expect that any type of flow of the suspension liquid, as long as it resulted in the mixing of the liquid would be sufficient to cause contact between the cells and the immobilized antigen.

Applicants assert that Simons does not render the claimed invention obvious. While both Simons and the present invention address the separation of fetal cells from a maternal blood sample, the technical solution provided by Simons is completely different from that of the present invention. Specifically, Simons depends on

the use of ligands that bind to antigens on *maternal* cells based on the assumption that, due to the mixed parentage of fetal cells, certain surface antigens present on maternal cells will be absent on fetal cells. Simons states, at column 5 lines 30-36:

> The method also does not attempt to distinguish the fetal cells based on "fetal" antigens such as fetal hemoglobin which may also be expressed by some maternal cells. In the present method, rather than selecting a fetal antigen that is present on some maternal cells (oncofetal antigens), the method utilizes a maternal antigen which is not present on any fetal cells.

For example, in Simons the maternal blood sample will be exposed to ligand toward a particular surface antigen, such as a HLA molecule. If that antigen is not expressed on the fetal cells, the fetal cells will not be bound and can be washed from the collecting surface. One might infer that the unbound cells may also contain maternal cells that for technical reasons did not adhere to the collector surface. More importantly, and as expressly addressed in Simons, since often maternal and fetal cells share HLA antigens, all cells in the maternal sample would bind to ligand, and the procedure would need to be repeated until a ligand directed to a distinguishing surface antigen is used (Simons, column 3 lines 17-48).

In contrast, the present invention uses a ligand specific for fetal cells for collection (claim 1 has been amended accordingly). While this method has the advantage of relying on an affirmative step (ligand binding), the problem of low incidence of fetal cells in the maternal circulation (approximately 1 cell in 100,000 according to the instant specification at page 2 lines 18-20) must be addressed. The use of chaotic advection to efficiently mix the sample without unduly stressing the blood cells provides the needed solution.

As evidence of the efficiency of chaotic advection for mixing in general and for rare cell separation in particular, Applicants invite the Examiner's attention to the following two references, attached hereto as Exhibits A and B.

Chaiken et al., 1986, "Experimental study of Lagrangian turbulence[1] in a Stokes flow," Proc. R. Soc. Lond. A 408:165-174 ("Chaiken," Exhibit A) relates to a laboratory demonstration of chaotic advection using a device having two cylinders, one placed within the other (as in the device used in the working examples of the instant specification), for studying chaotic advection and its ability to achieve efficient stirring in the laboratory. Gomez, 1999, "Attachment of Cells to Surfaces under Controlled Fluid Flows," Graduate Thesis, Columbia University ("Gomez," Exhibit B), published several years after filing the present application by a graduate student in Dr. Leonard's laboratory, illustrates the use of chaotic advection produced by such a device in separating out rare cells. Capture of murine B-cell hybridoma cells, diluted 1:100,000 with human red blood cells, achieved enrichment on the order of 60,000-fold, and collection of 11 out of 1000 rare cells present (Gomez et al., pp. 43-71).

Accordingly, the use of chaotic advection provides a means for directly collecting fetal cells in a maternal blood sample, and thus provides a single step alternative to the potentially multi-step method of Simons. Because Simons uses a completely different approach for collecting fetal cells (by binding maternal cells, the predominant cell type in the sample), it cannot render the claimed invention obvious. Accordingly, the rejection should be removed.

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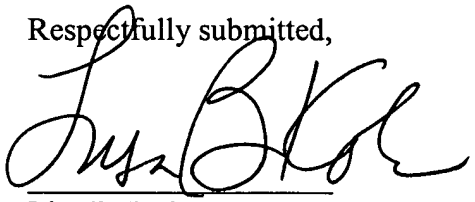
[1] "Lagrangian turbulence" is an alternate term for "chaotic advection", as set forth in Chaiken, page 166: "This process is sometimes referred to as 'chaotic advection' (Aref, 1984). A somewhat more general terminology that we also use here is that of 'Lagrangian turbulence,' implying the idea of chaos within the Lagrangian picture of fluid dynamics."

2. Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully request that all pending claims be deemed allowable.

Respectfully submitted,



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